Population analysis of paraquat toxicokinetics in poisoning patients

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Background and Objectives

Paraquat (PQ) is a commonly used herbicide that has caused many accidental or intentional deaths. Only a few studies have been done on PQ toxicokinetics (TK) in humans (1, 2). In this study a population TK analysis was performed to estimate the typical TK parameters and interindividual variability of PQ distribution in intoxicated patients. Potential covariates were explored as well.

Methods

• PQ plasma concentrations from 78 poisoning patients were used.
• A two-compartmental TK model with first-order absorption and first-order elimination was fitted to the data when choosing the basic structural model.
• An exponential model and combined model were used for inter-individual variability (IVV) and residual errors, respectively.
• The varying doses were imputed as covariates on the bioavailability factor.
• The median dose of PQ (10 g) was given as the amount administered to each patient.
• The logit of bioavailability factor (XF) was first estimated, and the bioavailability factor was subsequently regenerated using the following formula: F= XF/(1+XF).
• Kp was fixed to 1 h⁻¹ given that the reported mean T_{max} in human was 3 h.
• Model selection was based on objective function values, bootstrap derived standard errors, graphics and visual predictive checks (VPC).
• A TK model for PQ was developed using Phoenix NLME version 1.2.

Results

A total of 698 plasma concentrations from 78 PQ poisoning patients were included in TK analysis.

Table 1 Demographics of the patients enrolled in the population toxicokinetic study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Toxicokinetic study</th>
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<tbody>
<tr>
<td>Male/Female (n)</td>
<td>52/26</td>
</tr>
<tr>
<td>Age (y)</td>
<td>28 (14-76)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>51 (35-66)</td>
</tr>
<tr>
<td>sCr (mg/dl)</td>
<td>2 (0.3-12.6)</td>
</tr>
<tr>
<td>CLp (L/h)</td>
<td>1.89 (0.29-13.25)</td>
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<tr>
<td>Ingestion volume (ml)</td>
<td>50 (5-750)</td>
</tr>
<tr>
<td>Ingestion dose (g)</td>
<td>10 (1-150)</td>
</tr>
</tbody>
</table>

Conclusions

• PQ toxicokinetics were characterised using a 2-compartment disposition model with first order absorption and elimination.
• The discrepancy between the estimated value of V/F and those previously published could be due to the uncertainty in the ingested doses.
• The low CLp reflects the PQ induced renal impairment at long time after swallowing.

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Reference